



A new class of potent non-imidazole H₃ antagonists: 2-aminoethylbenzofurans

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Abstract—2-Aminoethylbenzofurans constitute a new class of H₃ antagonists that are more rotationally constrained than most previously reported H₃ antagonists. They retain high potency at human and rat receptors, with efficient CNS penetration observed in 35. The SAR of the basic amine moiety was compared in three different series of analogues. The greatest potency was found in analogues bearing a 2-methylpyrrolidine, a 2,5-dimethylpyrrolidine, or a 2,6-dimethylpiperidine.
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Histamine (1) is an important modulator of human and animal physiological processes.¹ Four distinct histamine receptor subtypes mediate the direct actions of histamine. H₁ receptors play a critical role in regulating inflammatory responses and CNS activity, and H₁ antagonists are used clinically to treat allergic asthma and rhinitis. H₂ receptors regulate gastric acid secretion, and H₂ antagonists are used clinically to treat excess acid production.² The newly discovered H₄ receptor is found in immune cells, suggesting a role in regulating inflammatory responses.³

The recent cloning of H₃ receptors from several species⁴ and the molecular characterization of H₃ receptors have provided new tools, and a clearer rationale, for a role for H₃ antagonists in treating human disease. Found on presynaptic nerve terminals, the H₃ receptor is constitutively active, and acts as a 'brake' on neurotransmitter release.⁵ H₃ antagonists relieve this inhibition, thereby elevating levels of histamine, acetylcholine, and other neurotransmitters. In animal models, H₃ antagonists have demonstrated efficacy in enhancing cognition and attention,⁶ regulating wakefulness and weight gain,⁷ and ameliorating allergic rhinitis⁸ (when coadministered with H₁ antagonists). However, in spite of the likely medical utility of H₃ antagonists, no agent in the class has yet received

clinical approval, perhaps due to inadequate drug-like properties.

The imidazole-based H₃ antagonists such as ciproxifan (2) and thioperamide (3) are useful tools and reference standards for pharmacological research,¹ but attention has been drawn to the potential liability of imidazole-containing compounds for clinical use, due to their potential to inhibit cytochrome-P₄₅₀ (CYP) drug metabolizing enzymes.⁸ This could then lead to drug–drug interactions by inhibiting the metabolism of co-administered drugs.⁹ For this reason, non-imidazoles have been targeted as potential drug candidates, and several distinct classes of non-imidazole H₃ antagonists have been produced (Fig. 1). Several of the most potent and promising classes of non-imidazoles such as 4¹⁰ (UCL-1972), 5¹¹ (UCL-2190), 6,¹² and 7¹³ (A-349821) share common structural features, namely, a basic amine connected through an alkoxy chain to a lipophilic group. Of these prototypes, the amino-propyloxy-aryl combination seen in compounds 5–7 may represent a privileged H₃ antagonist pharmacophore.^{1d,g}

A new class of H₃ antagonists, the 2-aminoethylbenzofurans (9) shown in Figure 2, was designed to give compounds more structurally rigidified than those comprising the established pharmacophore (8). By converting the proximal methylene in 8 to a sp² carbon, then connecting to the phenyl moiety through a newly created sp² carbon, the resulting benzofurans (9) remove two rotatable bonds. One goal was to enhance the

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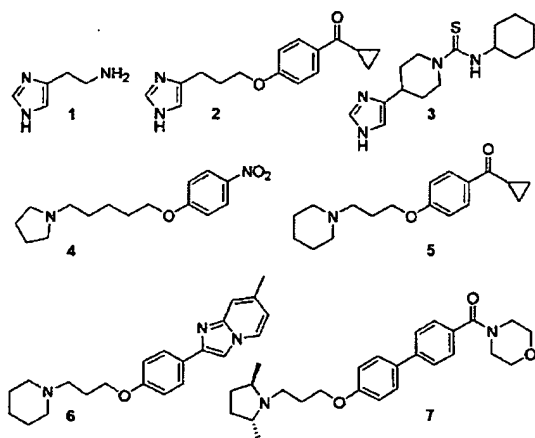


Figure 1. Structures of H_3 antagonists based on imidazoles (2, 3), and non-imidazole H_3 antagonists (4–7).

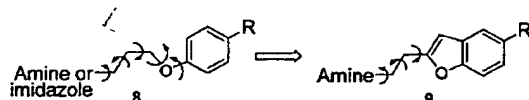


Figure 2. H_3 antagonists based on 2-aminoethylbenzofurans (9) have less conformational mobility than analogues (8) based on the 3-aminopropoxyphenyl skeleton.

selectivity of compounds for H_3 over other receptors. It has also recently been proposed that reductions in rotatable bond count are associated with improved absorption in vivo,¹⁴ and with increased drug-likeness.¹⁵

The synthesis of the target benzofurans required phenols 16–19 as starting materials (Fig. 3). While 19 is commercially available, and 18 was easily produced by amination of 17, the preparation of 16 required a multi-step sequence. By *trans*-lithiation of 10, then quenching with tri-isopropyl borate, the borate ester 11 was produced, which when treated acid produced the boronic acid 12. Suzuki coupling of 12 with 14 gave 15, which was deprotected with fluoride to give 16. By carefully controlled selective iodination of 16, 18, and 19 with sodium hypochlorite and sodium iodide at low temperature, good yields of the monoiodides 20–22 were produced. The palladium catalyzed Sonagashira–Stevens coupling products were readily cyclized to the 2-hydroxyethylbenzofurans 23–25 in high yields. For conversion to the final products (26–28), the alcohols were converted to the mesylates, which could be isolated in high yield, but typically were not purified, but reacted directly with target amines in CH_3CN at ambient temperature. For the most highly hindered amines, (2*R*,5*R*)-dimethylpyrrolidine and (*cis*-2,6)-dimethylpiperidine, heating at 80 °C for 2–48 h was required to induce displacement of the mesylates, and was accompanied by substantial amounts (50 and 90%, respectively) of the

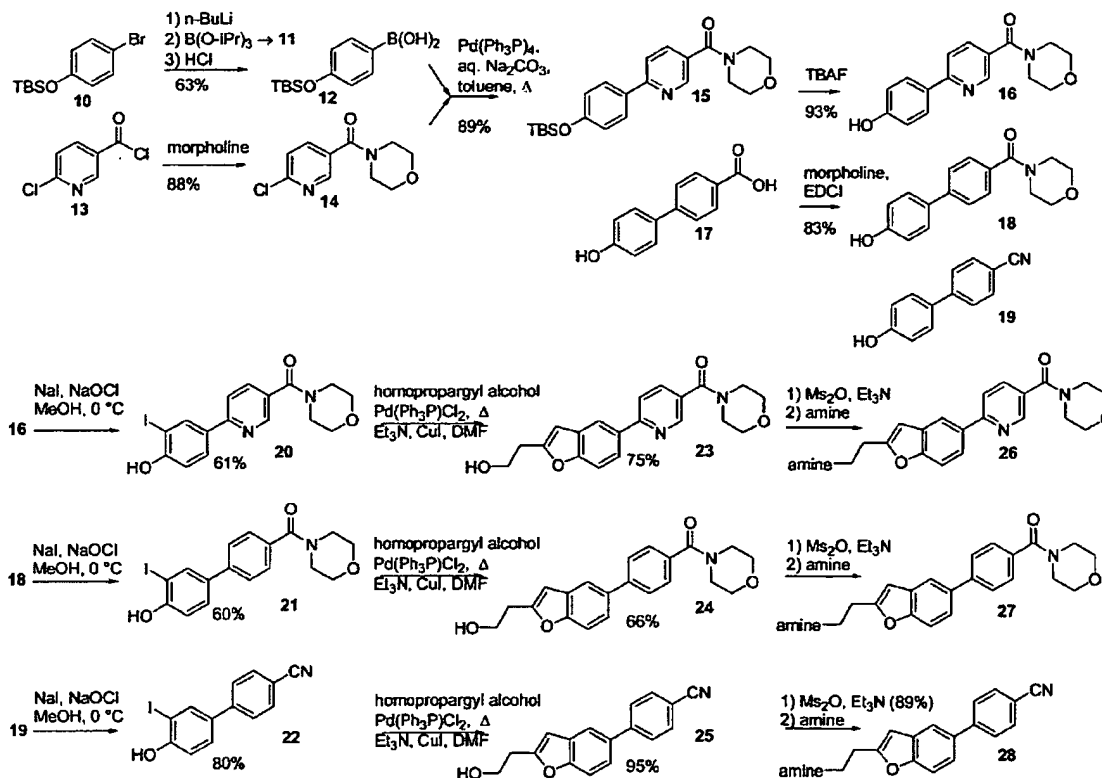


Figure 3. Synthesis of the 2-aminoethylbenzofuran H_3 antagonists.

styrene side product produced by E₂ elimination. Commercially available optically pure amines were used to prepare 30–34 and 37 in >96% e.e. Products were purified to >95% purity by reversed phase HPLC, eluting with acetonitrile/aqueous CF₃CO₂H.

As our ultimate goal was to find CNS drug candidates, we sought compounds with an ability to achieve selectively high brain concentrations, features associated with relatively high lipophilicity and low molecular weight. We also sought compounds combining comparable and high potency at both human and rat H₃ receptors (*K*_i < 10 nM), since this would enhance the likelihood that agents found potent and effective in the rat behavioral models would have similar effects in humans.

An assessment of the SAR of the basic amine moiety from the data in Table 1 shows that for compounds 29–38, all bearing the 4-cyanophenyl aromatic group, the pyrrolidine 29, the racemic 2-methylpyrrolidine 35 and 2-methylpiperidine 37, and (2*S*)-hydroxymethyl pyrrolidine 33 possessed the greatest potency (< 10 nM) at the human receptor, while only compound 35 possessed a similar degree of high potency at the rat receptor. Analogues bearing pyrrolidine rings with other polar substituents (30–32, 34), and polar heterocycles (36, 42, 45) all had lower H₃ potency. When the effects of the aro-

matic benzofuran ring substituents are compared in the compounds bearing identical amines in Table 1 (29 versus 43; 33 versus 39; 37 versus 44), there appears to be little effect of the aromatic ring on H₃ potency. Among chiral compounds, the (3*R*)-dimethylaminopyrrolidine 31 was slightly more potent than the (3*S*)-dimethylaminopyrrolidine 30. The (2*S*)-hydroxymethylpyrrolidines (33, 39) were much more potent than the (2*R*)-hydroxymethylpyrrolidines (32, 44). It might be anticipated that the potency of racemic 35 still could be increased further with the synthesis of the appropriate pure enantiomer. Since the absolute configuration of the most potent enantiomer of 2-hydroxymethylpyrrolidine (2*S*)

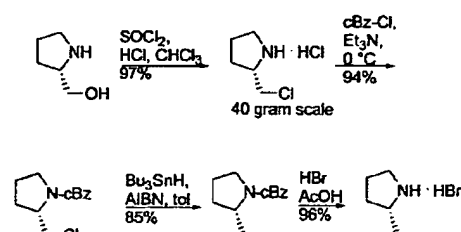


Figure 4. Synthesis of *R*-2-methylpyrrolidine.

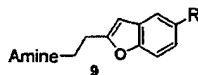
Table 1. SAR of compounds of general structure 9, varying the aromatic substituent R, and the amine moiety

9

Compd		Human H ₃		Rat H ₃	
		K _i nM	pK _i ± SEM	K _i nM	pK _i ± SEM
Ar substituent R → Ph(4-CN)					
Amine ↓					
Pyrrolidine	29	4.2	8.37 ± 0.07	47	7.33 ± 0.04
(3 <i>S</i>)-Dimethylaminopyrrolidine	30	49	7.31 ± 0.03	140	6.86 ± 0.07
(3 <i>R</i>)-Dimethylaminopyrrolidine	31	16	7.80 ± 0.09	63	7.20 ± 0.16
(2 <i>R</i>)-Hydroxymethylpyrrolidine	32	18	7.75 ± 0.19	160	6.78 ± 0.13
(2 <i>S</i>)-Hydroxymethylpyrrolidine	33	2.2	8.65 ± 0.04	26	7.59 ± 0.08
(2 <i>R</i>)-Carboxymethylpyrrolidine	34	320	6.50 ± 0.20	1600	5.79 ± 0.20
(±2)-Methylpyrrolidine	35	0.95	9.02 ± 0.06	6.5	8.19 ± 0.11
<i>N</i> -Imidazolyl	36	600	6.22 ± 0.12	2200	5.66 ± 0.14
(±2)-Methylpiperidine	37	5.8	8.23 ± 0.10	45	7.35 ± 0.09
(Δ3,4)-Tetrahydropyridine	38	10	7.99 ± 0.17	50	7.30 ± 0.20
Ph(4-CO morpholine)					
(2 <i>S</i>)-Hydroxymethylpyrrolidine	39	1.9	8.72 ± 0.04	6.9	8.16 ± 0.06
(±2)-Methylpiperidine	40	3	8.52 ± 0.19	14	7.87 ± 0.20
(Δ3,4)-Tetrahydropyridine	41	5.9	8.23 ± 0.25	17	7.77 ± 0.16
Morpholine	42	45	7.35 ± 0.20	160	6.79 ± 0.22
Pyridine(4-CO morpholine)					
Pyrrolidine	43	3.9	8.4 ± 0.25	29	7.53 ± 0.24
(2 <i>R</i>)-Hydroxymethylpyrrolidine	44	36	7.44 ± 0.32	110	6.96 ± 0.24
Morpholine	45	150	6.83 ± 0.17	260	6.59 ± 0.08

Binding potencies were assessed by displacement of ³H-N-α-methyl histamine. The human H₃ values were from cloned human H₃ expressed in C6 cells, while rat H₃ values were from rat cortical membranes. p*K*_i = −log*K*_i. The number of independent p*K*_i determinations was ≥ 3 for all compounds.

Table 2. SAR of compounds of general structure 9, varying the aromatic R substituent, and the amine moiety



Amine	#	Ph(4-CN)				Ph(4-COMorpholine)				Pyridine(4-COMorpholine)			
		Human H ₃		Rat H ₃		Human H ₃		Rat H ₃		Human H ₃		Rat H ₃	
		K _i nM	pK _i ±SEM	K _i nM	pK _i ±SEM	K _i nM	pK _i ±SEM	K _i nM	pK _i ±SEM	K _i nM	pK _i ±SEM	K _i nM	pK _i ±SEM
(2)-Methylpyrrolidine	46	0.45	9.35±0.04	3.22	8.49±0.04	53	0.7	9.15±0.06	2	8.71±0.04	60	0.55	9.26±0.06
(2 <i>R</i> ,5 <i>R</i>)-Dimethylpyrrolidine	47	5.1	8.29±0.00	42	7.38±0.04	54	2.2	8.65±0.22	6.9	8.16±0.17	61	5.9	8.23±0.23
(3 <i>R</i>)-Hydroxypyrrolidine	48	8.8	8.05±0.03	95	7.02±0.08	55	6.2	8.21±0.15	35	7.46±0.20	62	12	7.93±0.21
Piperidine	49	8.8	8.06±0.02	59	7.23±0.13	56	2.3	8.64±0.20	6.2	8.21±0.18	63	12	7.9±0.25
(<i>cis</i> -2,6)-Dimethylpiperidine	50	2.4	8.62±0.06	22	7.67±0.08	57	1.2	8.92±0.23	6.6	8.18±0.21	64	5.6	8.25±0.2
4-Methylpiperidine	51	15	7.82±0.14	16	7.79±0.20	58	17	7.76±0.25	43	7.37±0.17	65	87	7.06±0.26
Hexahydroazepine	52	7.8	8.11±0.14	44	7.36±0.25	59	3.5	8.46±0.24	10	8.0±0.18	66	16	7.8±0.26

*Compound determined to be 99.9% e.e. by chiral HPLC analysis of the 1-tartrate salt.

corresponds to the (2*R*) configuration of 2-methylpyrrolidine, the reported¹⁶ synthesis of (2*R*)-methylpyrrolidine from (2*S*)-prolinol (>99% e.e.) was completed on a large scale as shown in Figure 4. High yields were obtained even when conducted on a 40 gram scale. This amine was then used to prepare 46 and 60, bearing the 2*R*-methylpyrrolidine as the basic amine.

A comparison of the SAR of amine substituents in three different aromatic substituted series (26–28) is shown in Table 2. The amines in Table 2 were selected based on the characteristics likely to induce the highest potency among the compounds (29–45), that is, cyclic 5, 6, or 7-membered amines, especially *ortho*-methyl substituted amines. The targeted compounds were indeed potent; for example, incorporation of the (2*R*)-methylpyrrolidine in the 4-cyanophenylbenzofuran series gave the highly potent analogue 46 with K_i values of 0.45 nM at the human H₃ receptor, and 3.2 nM at the cortical rat H₃ receptor (1.35 nM at cloned rat H₃R). Thus 2-methylpyrrolidine induced high potency in all series (analogues 46, 53, 60), as did (2*R*,5*R*)-dimethylpyrrolidine (analogues 47, 54, 61). Similarly, (*cis*-2,6)-dimethylpiperidine (analogues 50, 57, 64) induced high potency in all series, as did unsubstituted piperidine (49, 56, 63). Piperidine itself has long been known to induce high H₃ potency in disparate H₃ antagonist series.^{10–13}

In comparing the SAR of the aromatic substituent, it is seen that the cyanophenyl analogues (46–52) had comparable potency to the phenylcarbonylmorpholine analogues (53–59). The pyridinecarbonylmorpholines (60–66) are heterocyclic aza analogues of 53–59, and some potent analogues are potent, such as 60, but in compounds 62–66 there appears to be a tendency for this series to have somewhat weaker potency.

Of the nine compounds which met the criteria for high potency (K_i <10 nM) at human and rat H₃R, and a

desirable balance of affinity to both receptors (ΔpK_i <1), analogue 35 and its pure enantiomer 46 were judged most likely to penetrate the BBB efficiently and achieve high CNS concentrations, compared to blood levels. This assessment was based on the higher lipophilicity of 35 (CLogP=5.2), compared to benzamide analogues like 53 (CLogP=4.3), or pyridineamide analogues like 60 (CLogP=2.1). Indeed, racemic compound 35 was found to efficiently penetrate CNS tissues, with brain:plasma ratios >30×, and very high brain concentrations were achieved (15,000 ng/gm) after iv dosing of 35 at 5 mg/kg.

The in vitro, metabolic, pharmacokinetic, and in vivo behavioral pharmacological profile of compounds in this series will be fully described elsewhere, but the data described here show that the new series of benzofuran-based H₃ antagonists contains compounds that achieve high CNS concentrations, as well as balanced nanomolar potency at both human and rat H₃ receptors.

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